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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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GTC BIOTHERAPEUTICS, INC.
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EXAMINER

AFREMOVA, VERA

ART UNIT PAPER NUMBER

1651

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM-

Office Action Summary

Application No.

09/927,824

Applicant(s)

GAVIN ET AL.

Examiner

Vera Afremova

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 June 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6,8-13,16-27,30 and 33 is/are pending in the application.
- 4a) Of the above claim(s) 27,30 and 33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-6,8-13,16-26 and 33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| <p>1) <input type="checkbox"/> Notice of References Cited (PTO-892)</p> <p>2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)</p> <p>3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>2/27/2004</u>.</p> | <p>4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____</p> <p>5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)</p> <p>6) <input checked="" type="checkbox"/> Other: <u>translation of 54 986,411</u></p> |
|---|--|

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/02/2004 has been entered.

Claims 7, 14, 15, 28, 29, 31, 32 and 34-44 were canceled by applicants.

Claims 1-6, 8-13, 16-27, 30, and 33 {as amended 12/04/2003} are pending and subject to restriction requirement.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-6, 8-13, 16-26 and 33, drawn to a method of preserving sperm using a cryoprotectant buffer and/or solution with glycerol, classified in class 435, subclass 2, for example.
- II. Claims 27, 30 and 33, drawn to a method of preserving sperm using a cryoprotectant buffer and/or solution lacking glycerol, classified in class 435, subclass 374, for example.

Claim 33 belongs to Group I as being dependent on claims 1, 13 or 24. Claim 33 belongs to Group II as being dependent on claim 27.

The inventions are distinct, each from the other because of the following reasons:

The methods of Group I and Group II are different because they comprise different active step of using different materials as claimed.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper. Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Byron V. Olsen on 8/13/2004 a provisional election was made to prosecute the invention of Group I, claims. Affirmation of this election must be made by applicant in replying to this Office action.

Claims 27,30 and 33 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 1-6, 8-13, 16-26 and 33 are under examination in the instant office action.

Claim Rejections - 35 USC § 112

Claims 1-6, 8-13, 16-26 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 13 and 24 are indefinite because they are confusing with regard to “first” and “second” temperature and with regard to “first” and “second” buffer/solution. It appears that “second” temperature of claim 1 is the “first” temperature of claim 13. The concept of temperature becomes even less clear when the protocol of cryopreservation recites “third” temperature and below. Identification of solutions/buffers as “first” and “second” is particularly uncertain because at least one of them contains glycerol and, thus, it is confusing when glycerol is added, what temperatures are required for equilibration with glycerol and what time is required for equilibration with glycerol. For example: claim 1 requires maintenance at second temperature for 4-21 hours but dependent claim 11 requires maintenance at the same second temperature for 7-20 minutes. Claim 13 indicates 4-21 time period for “first” temperature but the dependent claim 19 indicates 1.5-4 hours for “first” temperature. Claim 1 recites that first temperature of stage are need to avoid glycerol toxicity. However, glycerol is added in both first and seconds buffer/solution/sample of claims 13 and 21. Further, claim 23 recites 7-20 minutes that are already totally uncertain what for.

Thus, it is unclear what are “first” and “second” phases as intended.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3-6, 8-13 and 16-26 are rejected under 35 U.S.C. 102(b) as anticipated by SU 986, 411 {IDS reference} or, in the alternative, under 35 U.S.C. 103(a) as obvious over SU 986, 411 in view of US 3,940,943 {IDS reference} and Royere et al. {IDS reference}.

Claims are directed a method of preserving mammalian sperm and storing the sperm wherein the method encompasses step of slow cooling sperm to a first temperature between 2 degree C and 10 degree C , step of rapid freezing sperm at second temperature of about -60C to about -90C of the sperm. The cooling step comprises the use of a cryoprotectant buffer/solution/sample without glycerol and the freezing step comprises the use of a cryoprotectant buffer/solution/sample with glycerol for treating the sperm before freezing. The first solution (cooling stage to first temperature) does not contain glycerol, the second solution (added before freezing) contains glycerol. The sperm is cooled and/or hold at temperature above freezing for equilibration with glycerol for either 4-21 hours or 7-20 minutes or 1.5-4 hours. The sperm is hold at freezing temperature for about 7-20 minutes or 10-15 minutes. Some claims are further drawn to the use of 5-10% glycerol. Some claims are further drawn to the use of cryoprotectant buffer comprising egg yolk at concentration of 10-30 %, antibiotics, sugar, Tris

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buffer and citric acid. Some claims are further drawn to a method of making an animal by fertilizing an oocyte with the preserved sperm.

SU 986, 411 discloses a method of preserving mammalian or bovine sperm wherein the method comprises step of combining the sperm with a first cryoprotectant buffer containing egg yolk (page 4, par. 1), step of cooling the sperm to a first temperature of about + 4 degree C using a slow cooling rate of about 0.2 C to 0.5 C per minute over the period of about 3 hours (table 1) and/or cooling and holding at 4 C for about 3-3.5 hours (page 4, last par.), step of adding a second cryoprotectant buffer comprising 10% glycerol (page 4, last 2 lines), step of maintaining the cooled sperm with the glycerol containing cryoprotectant buffer for 30 minutes at refrigerator temperature (page 5, par. 2), step of freezing sperm in vapors of liquid nitrogen by maintaining or holding at second temperature of about -120 C to about -140 C for 8-8.5 minutes (page 3, last lines) and step of storing the sperm in liquid nitrogen or at the third temperature (page 5, par. 6). The cryoprotectant composition in the cited method comprises sugar including fructose, egg yolk and antibiotic "spermosan-3" (page 4, par. 1). Furthermore, the cited patent SU 98641 1 discloses steps of thawing the frozen sperm and using the stored sperm for oocyte fertilization (table 5), thereby making an animal within the meaning of the presently claimed invention.

Thus, the cited SU 986, 411 teaches the same or substantially similar active steps in the method for preserving mammalian sperm as the claimed method wherein both methods comprises same cooling rates and same temperatures in the absence of glycerol, same time and/or temperature for equilibration with glycerol and same freezing time and temperature with glycerol. Thus, the cited method appears to anticipate the claimed invention.

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Although the cited patent is silent about egg yolk concentration, it is common to use about 7.5-25% egg yolk in the sperm cryoprotectant composition as evidenced by US 3,940,943 (lines bridging col. 2 and col. 3). Although the cited patent is silent about Tris-citrate buffer, the egg yolk provides sufficient buffering effects. Moreover, the use of buffered yolk-citrate compositions a common practice as evidenced by Royere et al. (page 556, col. 2, par. 2).

Thus, the claimed method would have been obvious to those of ordinary skill in the art within the meaning of USC 103. Accordingly, the claimed invention as a whole was at least prima facie obvious, if not anticipated by SU 986411, especially in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6, 8-13, 16-26 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over SU 986, 411 in view of US 3,940,943 {IDS reference} and Royere et al. {IDS reference} taken with US 3,791,384 (IDS reference) and Ahmad et al. (PTO-892).

Claims 1-6, 8-13 and 16-26 as explained above. Claim 33 is further drawn to the use of specific antibiotics tylosin, gentamicin, lincospectin or spectinomycin in the cryoprotectant composition.

SU 986, 411 is relied upon as explained above methods for preservation of mammalian sperm by protocols encompassing slow cooling and rapid freezing of the sperm. Royere et al.

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and US 3,940,943 disclose the similar concepts of step-wise cooling and freezing of sperm. Royere et al. also teaches the concept of reducing possible toxic effects of glycerol by adding glycerol to the cooled sperm sample before freezing (page 556, col. 2, lines 8-10).

The references SU 986 411, US 3,940,943 and Royere et al. are lacking particular disclosure about the use of specific antibiotics. However, the reference by Ahmad et al. demonstrates the use of antibiotics tylosin, lincospectin and gentamicin in the solutions in the methods for preserving mammalian sperm (see abstract) together with egg-yolk-Tris components. The cited patent US 3,791,384 also teaches the use of other components in composition/solution for sperm preservation including Tris buffer, fructose, citric acid and antibiotics including streptomycin (col. 5, line 10-15; col. 2, lines 65-68 and col. 3, lines 1-5).

Therefore, it would have been obvious at the time the claimed invention was made to practice a mammalian sperm preservation method encompassing the use of slow cooling/rapid freezing of sperm and the addition of glycerol to the cooled sperm before freezing with a reasonably expectation in success for preserving the sperm intended for fertilization because substantially similar protocols have been taught and suggested in the prior art as adequately demonstrated by all cited references (SU 98641 1; US 3,940,943; Royere et al.). One of skill in the art would have been motivated to use typical cryoprotectant buffer formulations with egg yolks and glycerol for the expected benefits of sperm preservation intended for fertilization as demonstrated in the prior art (SU 98641 1; US 3,940,943; Royere et al.). One of skill in the art would have been motivated to add glycerol to the cooled sperm sample before freezing for the expected benefits in reducing possible toxic effects of glycerol on mammalian sperm (SU

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98641 1; Royere et al.). It would have been obvious at the time the claimed invention was made to add antibiotics and/or other components including Tris buffer and citric acid the cryoprotectant compositions intended for sperm preservation since all presently claimed ingredients are known and have been used for sperm preservation as adequately demonstrated by the cited references US 3,791,384 and Ahmad et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 12/04/2003 have been fully considered but they are not persuasive.

In response to applicant's argument that the cited references fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies such as "first" and "second" phases including temperature, rates, time solutions, samples, solutions or buffers are not clearly recited in the rejected claim(s) in order to distinguish from the prior art methods that also encompass the same or similar step-wise slow cooling and rapid freezing stages in the method of sperm cryopreservation.

With regard to the "new buffer" as argued it is noted that the claimed method encompasses that use of the same compositions that are commonly used in the methods for cryopreservation of sperm.

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Applicant's arguments do not comply with 37 CFR 1.111(c) because they do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited or the objections made. Further, they do not show how the amendments avoid such references or objections.

Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Vera Afremova

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August 20, 2004


VERA AFREMOVA
PRIMARY EXAMINER